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In vitro susceptibility of methicillin-resistant *Staphylococcus aureus* isolates from skin and soft tissue infections to vancomycin, daptomycin, linezolid and tedizolid

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ABSTRACT

Introduction: Treatment of multidrug-resistant Gram-positive infections caused by *Staphylococcus aureus* remains as a clinical challenge due to emergence of new resistance mechanisms. Tedizolid is a next-generation oxazolidinone, recently approved for skin and soft tissues infections. We conducted a study to determine *in vitro* susceptibility to vancomycin, daptomycin, linezolid and tedizolid in MRSA clinical isolates from adult patients with skin and soft tissue infections.

Material and methods: Methicillin-resistant *S. aureus* isolates were collected in three tertiary-care hospitals of Medellin, Colombia, from February 2008 to June 2010 as part of a previous study. Clinical characteristics were assessed by medical records and MIC values were determined by Epsilometer test. Genotypic analysis included *spa* typing, MLST, and SCC*mec* typing.

Results: A total of 150 MRSA isolates were evaluated and tedizolid MIC values obtained showed higher *in vitro* activity than other antimicrobials, with MIC values ranging from 0.13 μg/mL to 0.75 μg/mL and lower values of MIC_{50} and MIC_{90} (0.38 μg/mL and 0.5 μg/mL). In contrast, vancomycin and linezolid had higher MIC values, which ranged from 0.5 μg/mL to 2.0 μg/mL and from 0.38 μg/mL to 4.0 μg/mL, respectively. Tedizolid MICs were 2- to 5-fold lower than those of linezolid. Clinical characteristics showed high previous antimicrobial use and hospitalization history. The majority of the strains belong to the CC8 harboring the SCC*mec* IVc and were associated with the *spa* t1610 (29.33%, $n = 44$).

Conclusion: In vitro effectiveness of tedizolid was superior for isolates from skin and soft tissue infections in comparison with the other antibiotics evaluated. The above added to its less toxicity, good bioavailability, daily dose and unnecessity of dosage adjustment, make tedizolid in a promising alternative for the treatment of infections caused by MRSA.

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Introduction

Staphylococcus aureus is one of the most important pathogens in humans, being responsable for various types of infections in the healthcare and community settings.[1,2] Among of these, skin and soft tissue infections (SSTIs) play an important role, not only by their high frequency but also due to severe forms that affect deep tissues, causing serious implications as high morbidity rates and increased hospital stay and costs.[1,3]

This microorganism is characterized by its high capacity to adapt to antimicrobials by the acquisition of several resistance mechanisms.[2–4] Particularly, the emergence of methicillin-resistance isolates (MRSA) has limited therapeutic options, because this resistance involves low affinity for all β-lactam antibiotics.[5]

Vancomycin has been considered an effective option for the treatment of skin and soft tissue infections caused by MRSA. However, the high burden of these infections in hospitals has led to overuse of this antibiotic which in turn has led to increased values of minimum inhibitory concentration (MIC), emergence of intermediate and total resistance to this antimicrobial and increased mortality.[6–8]

This situation underscores the need for new antimicrobial options to the treatment of infections caused by MRSA which respond to changing resistance patterns.[8] Currently, the therapeutic options approved by Food and Drug Administration (FDA) for the SSTIs by MRSA include daptomycin, linezolid, and the recently introduced, tedizolid.[9,10]

Tedizolid is a novel oxazolidinone with high potential of action that is approximately four times more potent than linezolid.[9,10] Although the mechanism of action is similar to other oxazolidinones, tedizolid has shown more advantages, as lower adverse effects over short courses of therapy and favorable pharmacokinetics.[9–11] Tedizolid shows an increased activity against species of staphylococci and enterococci, including drug-resistant MRSA and vancomycin- and linezolid-resistant phenotypes.[9–11]

Constant changes in the epidemiology of infections caused by *S. aureus* reaffirm that this microorganism is a major threat for public health and highlights the need to evaluate therapeutic alternatives that allow for a better prognosis of these infections.

In Colombia, MRSA (both healthcare-associated and community-associated) has become a worrisome clinical problem, with a general frequency of 27%, reaching in some cities up to 50%.[12] This situation brings about new challenges for the treatment of this infections and patient safety.

Therefore, the aim of this study was to determine *in vitro* susceptibility to vancomycin, daptomycin, linezolid and tedizolid of MRSA clinical isolates from patients with skin and soft tissue infections, collected in three tertiary-care hospitals of Medellin, Colombia.

Material and methods

Bacterial isolates

Methicillin-resistant *S. aureus* isolates were collected in three tertiary-care hospitals of Medellin, Colombia, from February 2008 to June 2010, as part of a previous cross-sectional study.[13–15] Hospitals A and B are hospitals with high level of complexity with 754 and 286 beds, respectively, which provide services in all medical specialties; whereas hospital C is a 140-bed cardiology hospital.

Clinical and epidemiological information

Clinical and epidemiological data were obtained from medical records. Information included demographic aspects, medical history, comorbidities, length of hospital stay and outcomes at discharge. Infections were classified as community-associated (CA-MRSA) or healthcare-associated (HA-MRSA), according to definitions established by the CDC.[16]

The research protocol was approved by the Bioethics Committee for human Research at Universidad de Antioquia (CBEIH_SIU-approval No. 0841150).

Strains and antibiotic susceptibility

The identification of *S. aureus* was conducted by standard laboratory methods based on colony morphology in sheep blood agar and phenotyping methods such as catalase and coagulase. Antibiotic susceptibilities of *S. aureus* isolates were assessed in accordance with Clinical Laboratory Standards Institute guidelines (CLSI, 2009) using a VITEK-2® instrument (bioMérieux Lyon, France). The Antibiotics evaluated included clindamycin, erythromycin, gentamicin, linezolid, moxifloxacin, oxacillin, rifampin, tetracycline, tigecycline, trimethoprim-sulfamethoxazole and vancomycin.

Evaluation of the susceptibility through Epsilometer test

The MICs to vancomycin, daptomycin, linezolid and tedizolid were determined using the Epsilometer test method (E-test) according to the manufacturer's instructions (Etest® bioMérieux and Liofilchem® MIC Test Strip). MIC_{50} and MIC_{90}, that correspond respectively to the 50% and the 90% of strains inhibited by a specific concentration of each antibiotic were obtained. The MIC breakpoints were determined according to the criteria defined by CLSI, 2016 as follows: for vancomycin, values less than or equal to 2 μg/ml, between 4 and 8 μg/ml, or greater than or equal to 16 μg/ml were considered susceptible, intermediate and resistant, respectively; for daptomycin, these values were less than or equal to 1 μg/ml for susceptibility and higher values were deemed as non-susceptible; for linezolid, values less than or equal to 4 μg/ml were deemed susceptible and greater than or equal to 8 μg/ml resistant; finally, for tedizolid, values less than or equal to 0.5 μg/ml were considered susceptible, 1 μg/ml intermediate and values higher than or equal to 2 μg/ml resistant. Strain ATCC 29213 of *S. aureus* was used as a control strain.

Molecular characterization

Presence of the species-specific *nuc* and *fem*A genes, as well as the *mec*A gene (determinant of methicillin resistance) were verified by polymerase chain reaction (PCR) as previously